Preface to Special Topic: Multiphase Microfluidics

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The formation and manipulation of fluid-fluid interfaces in the form of microscopic drops and bubbles within microfluidic systems have made paradigm-shifting advances in the way chemical and biological experiments are conducted by enabling massively parallelized yet exquisitely controlled compartmentalization and automated analysis of chemical experiments. The ability to screen thousands of chemical and/or physical transformations per day is of much value in a variety of scientific contexts—from the screening of rare mutation events in DNA or discovery of active catalysts for chemical transformations to the search for optimal conditions for protein crystallization. Furthermore, a hitherto unachievable level of precision in the generation of fluid-fluid interfaces enabled by microfluidics has opened up entirely new vistas in the synthesis of structured, functional micro- and nano-scale materials for a broad spectrum of applications. Multiphase microfluidics is, therefore, a rapidly advancing area of interdisciplinary scientific investigation and technological innovation. I am thoroughly delighted to edit this special topics section and thankful to Dr. Leslie Yeo for giving me the opportunity to do so. We have a collection of nine papers in this section that span both the fundamentals and frontier applications of this exciting research field.

The sheer variety of observable fluid structures and dynamic phenomena when two or more fluids are injected into microchannels means that detailed physical understanding of droplet formation, flow, and packing are crucial for the systematic development and optimization of device geometries and experimental protocols. Vuong and Anna[1] present a detailed examination of the structure and packing of bubbles (or drops) downstream of the dispensing region in a microfluidic device. They use geometrical arguments, independent of fluid properties, to predict transitions between various bubbly structures and validate their predictions for both bubble and droplet systems generated from three "canonical" dispensing geometries. This work provides valuable design parameters for the rational tuning of multiphasic structures within microchannels. Cubaud, Sauzade, and Sun[2] study dynamical transitions and systematically map morphological regimes in gas-liquid flow when a dissolving gas (such as CO_2) is used, where mass transfer of gas into the liquid occurs concurrently with bubble formation and flow. This study of "carbonated" microflows is a growing area of research with very practical implications in several areas, ranging from geochemistry in sub-surface reservoirs to bio-fluid mechanics and fuel cell technology. The exquisite control over multiphase interfaces possible in microfluidic devices further enables the fabrication of functional microscale materials simply by photopolymerizing the dispersed fluids. Kantak *et al.*[3] present the first demonstration of a Förster resonance energy transfer (FRET)-based *in vitro* glucose assay entirely encapsulated within photopolymerized spherical microparticles fabricated using droplet microfluidics. Such functional microparticles can be used as low cost yet sensitive *in vitro* biosensors for a variety of applications requiring spatially resolved sensing, such as cell culture and tissue engineering.

Compartmentalization and parallelization of chemical experiments within microscale droplets have been the primary drivers for the rapid development of multiphase microfluidics. Technologies employing droplet-based "digital" biology to accomplish qPCR, high-throughput sequencing, and screening assays have been successfully commercialized in recent times. There is still considerable room for further exploration in this domain. Yashina, Meldrum, and deMello[4] use droplet-based compartmentalization to demonstrate an elegant method of studying the complex and

poorly characterized polymorphic behaviour of a very important biomineral—calcium carbonate. They use segmented droplet microfluidics to precisely and robustly control calcium carbonate crystallization and, crucially, demonstrate the ability to direct the polymorphic form of calcium carbonate crystals between calcite and vaterite. Polymorphism in inorganic and organic (molecular) crystals is an important and rapidly expanding area of research, with broad implications in, for example, pharmaceutical processing and drug formulation. Droplet-based microfluidics has also opened up new frontiers for spatially and temporally addressed *in vitro* exploration of biological phenomena within living cells, which are characterized by complex, heterogeneous biochemical milieus that are difficult to mimic with conventional *in vitro* experimental methods. Dammann, Nöding, and Köster[5] present a droplet-based scheme to study network formation of an important cytoskeletal protein—vimentin—in the presence of divalent magnesium ions. Using a novel scheme of calibration and data analysis, they demonstrate correlation of the chemical contents of any individual droplet (which cannot be directly visualized) with the relevant biological phenomenon under observation, in this case—the formation of vimentin aggregates. Biological assays employing functional nano- and micro-particles have gained prominence in recent years. Such assays typically involve several steps such as binding, incubation, and separation involving significant skilled user input and protocol optimization, all of which can potentially be automated in serial fashion on droplet-based microfluidic platforms. Kurup and Basu describe an exciting *field-free* method of microparticle concentration within droplets that essentially relies on competition between hydrodynamic drag and sedimentation under gravity within droplets.[6] They analyse the relevant physics and arrive at a dimensionless parameter predicting device performance, which depends on the key operating parameters and can be directly used in design and optimization studies. Long-term robustness and reproducibility of operation are crucial issues as the idea of compartmentalized chemistry moves beyond proof-of-concept applications. In this context, Elvira *et al*.[7] present a detailed examination of droplet dispensing robustness in "digital" microfluidic devices, involving electrowetting-driven migration of droplets from reservoirs, and outline a set of key design considerations based on device and operating parameters.

"Soft" and diffuse fluid interfaces, obtained for example in aqueous two-phase systems (ATPS) comprised by aqueous mixtures of incompatible polymers such as polyethylene glycol (PEG) and dextran, are of much interest in the development of all-aqueous multiphase microfluidic strategies that provide mild and biocompatible environments for a variety of applications such as biochemical separations, microparticle fabrication, etc. In the first of two papers on this topic, Geschiere *et al*.[8] provide experimental evidence of a fascinating and counterintuitive fluid phenomenon—retarded instability of fluid threads of an aqueous polymer solution (PEG) when dispensed into another aqueous solution of an incompatible polymer (dextran). This study, besides provoking interest from a fundamental fluid physics standpoint, has important practical implications in the design of microfluidic devices that involve breakup of fluid threads with very low interfacial tensions and diffuse fluid interfaces. Lee *et al*.[9] generate biphasic aqueous droplets containing PEG and dextran in an immiscible oil and demonstrate tunable internal droplet morphologies ranging from near-equilibrium structures to non-equilibrium structures that can potentially be used for *in vitro* biochemical experimentation in complex, crowded, and biomimetic milieus.

Finally, I gratefully acknowledge the generous and timely assistance of Linda Boniello and the entire production staff of *Biomicrofluidics* during all stages of execution for this special topics section. I hope you enjoy reading this collection of papers and that it offers new perspectives, raises intriguing questions, and sparks new investigations.

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